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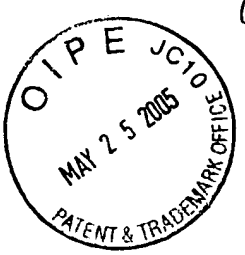

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Oliver Gierke
(Type or print name of person mailing paper or fee)

Oliver Gierke
(Signature of person mailing paper or fee)

RE: U.S. Patent No. 6,143,771
Title: Compounds
Inventors: Per Lennart Lindberg and Sverker von Unge
Assignee: AstraZeneca AB
Ref: 1103326-0793

The following are enclosed:

- Application for Extension of Patent Term Under 35 U.S.C. § 156: Original and four copies
- Exhibit A: U.S. Patent No. 6,143,771
- Exhibit B: Certificate of Correction dated May 8, 2001
- Exhibit C: Maintenance Fee Payment Statement
- Exhibit D: Copy of Terminal Disclaimer dated November 15, 1999
- Exhibit E: Copy of Terminal Disclaimer dated April 28, 2000
- Exhibit F: Patent Claim Coverage of Approved Product
- Exhibit G: Chronology of Significant Activities: IND 64,865 and NDA 21-689
- Return postcard.

Respectfully submitted,

Leslie Morioka
Reg. No. 40,304

Attorney for Applicant(s)
Attorney's Direct Telephone: 212-819-8276
Customer No. 007470
(212) 819-8200

Enclosures

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	**US 6,143,771**
Issued:	**November 7, 2000**
To:	**Per Lennart Lindberg; Sverker von Unge**
For:	**COMPOUNDS**

"EXPRESS MAIL" Label No. EV585054408US
Date of Deposit May 25, 2005
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Name of person mailing the paper and fee

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

TABLE OF CONTENTS

Exhibits

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Sir:

Applicant, AstraZeneca AB, a corporation organized and existing under the laws of Sweden, the address of which is S-151 85 Södertälje, Sweden, represents that it is the owner and assignee of the entire interest in and to Letters Patent of the United States No. 6,143,771, granted to Per Lennart Lindberg and Sverker von Unge on the 7th day of November, 2000, for COMPOUNDS by virtue of assignment from Per Lennart Lindberg and Sverker von Unge to Astra AB, recorded April 17, 1995, at Reel 7438, Frame 0120, and from Astra AB to AstraZeneca AB, recorded September 25, 2000, at Reel 011219, Frame 0749.

The holder of marketing approval for Nexium® I.V. (esomeprazole sodium for injection, 20 and 40 mg), the Approved Product that is relevant to this application, is AstraZeneca LP. AstraZeneca LP and AstraZeneca AB are both owned by AstraZeneca PLC, headquartered in London, England.

Applicant, through its duly authorized attorney, hereby submits this application for extension of patent term under 35 U.S.C. § 156 by providing the following information required by the statute and by the Rules of Practice in Patent Cases, 37 C.F.R. § 1.740. For the convenience of the United States Patent and Trademark Office, the information in this application is presented in the order set forth in Section 1.740 of the Rules.

1. Identity of the Approved Product (37 C.F.R. § 1.740(a)(1))

Pursuant to 37 C.F.R. § 1.740, the chemical and generic name, physical structure or characteristics of the Approved Product, Nexium® I.V. (esomeprazole sodium for injection, 20 and 40 mg), are as follows:

Nexium® I.V. contains, as the active ingredient, esomeprazole sodium, which is the sodium salt of the S-isomer of omeprazole. The chemical name of esomeprazole sodium is S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium.

2. Identity of Federal Statute Under Which Regulatory Review Occurred (37 C.F.R. § 1.740(a)(2))

The Approved Product is a drug product and the submission was approved under Section 505(b) of the Federal Food, Drug, and Cosmetic Act ("FDCA") (21 U.S.C. § 355(b)).

3. Identity of Date on Which Approved Product Received Permission for Commercial Marketing or Use (37 C.F.R. § 1.740(a)(3))

The Approved Product received permission for commercial marketing or use in a letter dated March 31, 2005, from Joyce Korvick, M.D., M.P.H., Acting Director, Division of Gastrointestinal & Coagulation Drug Products, Office of Drug Evaluation III, Center for Drug Evaluation and Research, U.S. Food and Drug Administration.

4. Identity of Active Ingredient (37 C.F.R. § 1.740(a)(4))

Applicant avers that the active ingredient of the Approved Product is esomeprazole sodium. Esomeprazole sodium has not been previously approved for commercial marketing or use under the FDCA. Please note that esomeprazole sodium is a different active ingredient from omeprazole, which is marketed as Prilosec® (NDA 19-810), for which a patent term extension has previously been granted. Esomeprazole sodium is also a different active ingredient from esomeprazole magnesium, which is marketed as Nexium® (NDA 21-153, NDA 21-154), and from omeprazole magnesium (NDA 21-229), which is marketed as Prilosec® OTC, for which products patent term extension applications are pending.

5. Timely Filing of This Application (37 C.F.R. § 1.740(a)(5))

This application is filed, pursuant to 35 U.S.C. § 156(d)(1) and 37 C.F.R. § 1.720(f), within the permitted sixty-day (60-day) period that began on March 31, 2005, the date the product received permission under 21 U.S.C. § 355(b), and that will expire on May 30, 2005.

6. Identity of the Patent for Which an Extension Is Sought (37 C.F.R. § 1.740(a)(6))

Inventors:	**Per Lennart Lindberg; Sverker von Unge**
Patent No.:	**6,143,771**
Issued:	**November 7, 2000**
Expiration:	**May 27, 2014**

7. Copy of Patent Attached (37 C.F.R. § 1.740(a)(7))

A copy of US 6,143,771, for which an extension is being sought, is attached in its entirety as Exhibit A. This patent is due to expire on May 27, 2014.

8. Disclaimers, Certificates of Correction, Receipts of Maintenance Fee Payment or Reexamination Certificate (37 C.F.R. § 1.740(a)(8))

A copy of a certificate of correction dated May 8, 2001, is attached as Exhibit B. A statement showing maintenance fee payment for pay year 04 is attached as Exhibit C. Maintenance fee payments for pay years 08 and 12 are not yet due. A copy of a terminal disclaimer dated November 15, 1999, is attached as Exhibit D. A copy of a terminal disclaimer dated April 28, 2000, is attached as Exhibit E. No reexamination certificate has been issued with respect to the patent.

9. Statement of Patent Claim Coverage of Approved Product (37 C.F.R. § 1.740(a)(9))

US 6,143,771 claims the Approved Product and methods of using and manufacturing the Approved Product, as shown in Exhibit F. Exhibit F presents a chart showing each applicable

patent claim (claims 1, 2 and 4 – 12) and the manner in which each such applicable patent claim reads on the Approved Product, method of using or method of manufacturing the Approved Product.

10. Statement of Relevant Dates and Information Pursuant to 35 U.S.C. § 156(g) (37 C.F.R. § 1.740(a)(10))

NDA 21-689 was submitted and approved for Nexium® I.V. The relevant dates are as follows:

a. Effective Date of the Investigational New Drug (IND) Application: June 21, 2002

b. IND Number: 64,865

c. Date on which the NDA was initially submitted: September 10, 2003

d. NDA Number: 21-689

e. Date on which the NDA was approved: March 31, 2005

11. Brief Description of Significant Activities Undertaken by Marketing Applicant During Applicable Regulatory Review Period and Respective Dates (37 C.F.R. § 1.740(a)(11))

Attached as Exhibit G is a brief description of the significant activities undertaken by the marketing applicant with respect to Nexium® I.V. during the regulatory review period for NDA 21-689, from October 25, 2001, to March 31, 2005.

12. Statement of Eligibility for Extension (37 C.F.R. § 1.740(a)(12))

Applicant believes that US 6,143,771 is eligible for extension under 35 U.S.C. § 156 because it satisfies all of the requirements for such extension as follows:

a. 35 U.S.C. § 156(a), 37 C.F.R. § 1.720

US 6,143,771 claims a product and a method of using that product.

b. 35 U.S.C. § 156(a)(1)

The term of US 6,143,771 will not have expired before submission of this application.

c. 35 U.S.C. § 156(a)(2)

The term of US 6,143,771 has never been extended under 35 U.S.C. § 156(e)(1).

d. 35 U.S.C. § 156(a)(3)

This application for extension is submitted by an attorney for the owner of record in accordance with the requirements of 35 U.S.C. § 156(d)(1)-(4) and rules of the U.S. Patent and Trademark Office.

e. 35 U.S.C. § 156(a)(4)

The Approved Product, Nexium® I.V., has been subject to a regulatory review period before its commercial marketing or use.

f. 35 U.S.C. § 156(a)(5)(A)

The commercial marketing or use of the Approved Product, Nexium® I.V., is the first permitted commercial marketing or use of the product under the FDCA (21 U.S.C. § 355(b)), under which such regulatory review period occurred.

g. **35 U.S.C. § 156(c)(4)**

No other patent has been extended for the same regulatory review period for the Approved Product, Nexium® I.V.

13. Statement as to Length of Extension Claimed and the Determination of Such Extension (37 C.F.R. § 1.740(a)(12))

In the opinion of the Applicant, US 6,143,771 is entitled to an extension of 793 days, pursuant to 35 U.S.C. § 156 and the implementing regulations, based upon the regulatory review period for Nexium® I.V.

The claimed length of this extension of 793 days was determined pursuant to 37 C.F.R. § 1.775 as follows:

(1) The regulatory review period under 35 U.S.C. § 156(g)(1)(B), which began on June 21, 2002, and ended on March 31, 2005, and lasted 1016 days, the sum of computations in (a) and (b) below:

(a) The period of review under 35 U.S.C. § 156(g)(1)(B)(i) began on June 21, 2002, and ended on September 10, 2003, a period of 447 days; and

(b) The period of review under 35 U.S.C. § 156(g)(1)(B)(ii) began on September 10, 2003, and ended on March 31, 2005, a period of 569 days;

(2) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in subparagraph 13(1) above (1016 days) less

(a) The number of days in the regulatory review period which were on or before the date on which the patent issued, November 7, 2000, which is zero (0) days, and

(b) The number of days during which applicant did not act with due diligence, which is zero (0) days, and

(c) One-half the number of days determined in subparagraph (13)(1)(a) (447) after subtracting the number of days determined in subparagraph (13)(2)(a) zero (0) and (b) zero (0), or 223 days, which leaves 793 days;

(3) The number of days as determined in subparagraph 13(2) in its entirety (793), when added to the original term of the patent, would result in the date July 28, 2016;

(4) Fourteen (14) years when added to the date of approval (March 31, 2005) would result in the date March 31, 2019;

(5) The earlier date as determined in subparagraphs (13)(3) and (13)(4) is July 28, 2016;

(6) Since the original patent issued after September 24, 1984, five (5) years are added to the original expiration date of the patent, resulting in a date of May 27, 2019; and

(7) The earlier of the dates obtained in subparagraph 13(5) and in subparagraph 13(6) is July 28, 2016.

Therefore, the length of extension of patent term claimed by applicant is 793 days, which is the period of time needed to extend the original expiration of term of May 27, 2014, until July 28, 2016.

14. Statement of Acknowledgment of Duty to Disclose Material Information (37 C.F.R. § 1.740(a)(13))

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought in this application.

15. Prescribed Fee (37 C.F.R. § 1.740(a)(14))

A check in the amount of $1,120.00, as prescribed in 37 C.F.R. § 1.20(j), is enclosed. Any additional necessary fees may be charged to Deposit Account 23-1703.

The PTO did not receive the following
listed item(s) cheque $1120

16. Contact Information (37 C.F.R. § 1.740(a)(15))

All inquiries and correspondence relating to this application for patent term extension should be directed to:

Leslie Morioka, Esq.
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White & Case LLP
1155 Avenue of the Americas
New York, NY 10036-2787
Tel.: (212) 819-8200
Fax: (212) 354-8113

Dr. Allen Giles, Esq.
Principal Patent Attorney
AstraZeneca Global Intellectual Property
Alderley Park
Macclesfield
Cheshire SK1O 4TG
United Kingdom
Tel: 011-44-625-516573
Fax: 011-46-8553-28820

17. Copies Enclosed (37 C.F.R. § 1.740(b))

Three duplicate copies of the present application papers are enclosed. The undersigned patent attorney certifies under penalty of perjury that the attached duplicates of the application papers are true and correct copies of such papers.

Respectfully submitted,

Dated: May 25, 2005

Leslie Morioka
Reg. No. 40,304

Attorney for Applicant

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New York, New York 10036
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Fax: (212) 354-8113
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EXHIBIT A

US006143771A

United States Patent [19]

Lindberg et al.

[11] Patent Number: 6,143,771

[45] Date of Patent: *Nov. 7, 2000

[54] COMPOUNDS

[75] Inventors: **Per Lennart Lindberg**, Mölndal; **Sverker von Unge**, Fjärås, both of Sweden

[73] Assignee: **AstraZeneca AB**, Sodertalje, Sweden

[*] Notice: This patent is subject to a terminal disclaimer.

[21] Appl. No.: **09/419,456**

[22] Filed: **Oct. 15, 1999**

Related U.S. Application Data

[63] Continuation of application No. 08/899,931, Jul. 24, 1997, abandoned, which is a continuation of application No. 08/376,512, Jan. 23, 1995, Pat. No. 5,714,504, which is a continuation-in-part of application No. 08/256,174, Jun. 28, 1994, Pat. No. 5,693,818.

[30] **Foreign Application Priority Data**

May 28, 1993 [SE] Sweden 9301830

[51] **Int. Cl.**[7] **A61K 31/44**

[52] **U.S. Cl.** **514/338**

[58] **Field of Search** 514/338

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,738,974	4/1988	Brandström	514/338
5,714,504	2/1998	Lindberg et al.	514/338
5,877,192	3/1999	Lindberg et al.	514/338
5,888,535	3/1999	Gray	424/449

FOREIGN PATENT DOCUMENTS

0005129	4/1981	European Pat. Off. .
0124495	1/1987	European Pat. Off. .
4035455	11/1990	Germany .
9501977	1/1995	WIPO .

OTHER PUBLICATIONS

Sverker von Unge et al., Stereochemical assignment of the enantiomers of omeprazole from X-ray fenchyloxymethyl derivative of (+)-(R)-omeprazole, *Tetrahedron: Asymmetry*, vol. 8, No. 12, p. 1997.

Cairns, et al. "Enantioselective HPLC determination . . . " Journal of Chromatography 8, 666 (1995) 323–328.

Yamada et al. "Synthesis and isomerization of optical active . . . " Chem. Pharm. Bull. 42(8) (1994) 1679–1681.

K. Miwa et al. Jpn. Pharmacol. Ther. "Proton pump inhibitor in rats, mice and dogs" 18 (1990) 165–187 (transl.).

H. Katsuki et al. "Determination of R(+)–and S(–)–Lansoprazole" Pharmaceutical Research 13(4) (1996) 611–615.

M. Tanaka et al. "Direct determination of pantoprazole enantiomers . . . " Anal. Chem. 68 (1996) 1513–1516.

P. Lindberg et al. "Omeprazole: The first proton pump inhibitor" Medicinal Res. Rev. 10 (1990) 2–50.

P. Lindberg et al. "The mechanism of action of . . . omeprazole" Journal of Medicinal Chemistry 29 (1986) 1327.

A. Brandsrom "Chemical reactions . . . " Reprint from Acta Chemica Scandinavica 43 (1989) 536–611.

K. Sigrist–Nelson et al. "Ro 18–5364, a potent inhibitor of the gastric (H^++K^+)–ATPase" Eur. J. Bioch. 166 (1987) 453.

CA 117:90292, Palomo et al.

Primary Examiner—Jane Fan

Attorney, Agent, or Firm—White & Case LLP

[57] **ABSTRACT**

The novel optically pure compounds Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} and $N^+(R)_4$ salts of (+)-5-methoxy-2-[[(4-methoxy-3, 5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or (–)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, in particular sodium and magnesium salt form thereof, where R is an alkyl with 1–4 carbon atoms, processes for the preparation thereof and pharmaceutical preparations containing the compounds as active ingredients, as well as the use of the compounds in pharmaceutical preparations and intermediates obtained by preparing the compounds.

12 Claims, No Drawings

COMPOUNDS

This application is a continuation of application Ser. No. 08/899,931, filed on Jul. 24, 1997, now abandoned which is a continuation application of Ser. No. 08/376,512, filed Jan. 23, 1995; now U.S. Pat. No. 5,714,504 which is a continuation-in-part of Ser. No. 08/256,174, filed Jun. 28, 1994 now U.S. Pat. No. 5,693,818.

FIELD OF THE INVENTION

The present invention is directed to new compounds of high optical purity and crystalline salts thereof, their use in medicine, a process for their preparation and their use in the manufacture of pharmaceutical preparation. The invention also relates to novel intermediates in the preparation of the compounds of the invention.

BACKGROUND OF THE INVENTION

The compound 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name omeprazole, and therapeutically acceptable alkaline salts thereof are described in U.S. Pat. No. 4,255,431 to Junggren et al., EP 5129 and EP 124 495, respectively. Omeprazole and its alkaline salts are effective gastric acid secretion inhibitors, and are useful as antiulcer agents. The compounds, being sulfoxides, have an asymmetric center in the sulfur atom, i.e. exist as two optical isomers (enantiomers).

The separation of the enantiomers of omeprazole in analytical scale is described in e.g. J. Chromatography, 532 (1990), 305–19 and in a preparative scale in DE 4035455. The latter has been done by using a diastereomeric ether which is separated and thereafter hydrolysed in an acidic solution. Under the acidic conditions needed for hydrolysis of the attached group, omeprazole is quite sensitive and the acid has to be quickly neutralized with a base to avoid degradation of the acid-sensitive compound. In the above mentioned application (DE 4035455) this is done by adding the reaction mixture containing concentrated sulfuric acid to a concentrated solution of NaOH. This is disadvantageous because there is a great risk of locally reaching pH values between 1–6, which would be devastating for the substance. Moreover, instantaneous neutralization will create heat which will be difficult to handle in large scale production.

There is no example in the known prior art of any isolated or characterized salt of optically pure omeprazole, i.e. of single enantiomers of omeprazole or of any isolated or characterized salt of any optically pure omeprazole analogue.

SUMMARY OF THE INVENTION

It is desirable to obtain compounds with improved pharmacokinetic and metabolic properties which will give an improved therapeutic profile such as a lower degree of interindividual variation. The present invention provides such compounds, which are novel salts of single enantiomers of omeprazole.

A preferred embodiment of the present invention provides pure crystalline enantiomeric salts of omeprazole and methods for the preparation thereof.

A more preferred embodiment of the present invention is directed to an optically pure crystalline enantiomeric magnesium salt of omeprazole and method for the preparation thereof.

A nonaqueous process according to the present invention is directed to the preparation of crystalline forms of an optically pure enantiomer of omeprazole magnesium salt or analogues thereof which includes steps of stirring a crude preparation of the omeprazole enantiomer under nitrogen into a methanolic magnesium methoxide solution, precipitating inorganic magnesium salt with addition of a small amount of water, removing any precipitated inorganic magnesium salts, concentrating the residual methanolic solution, precipitating the omeprazole enantiomer by adding acetone to the residual solution, and filtering off the optically pure enantiomer crystals of magnesium omeprazole or analogues thereof.

The present invention in a further aspect provides a novel method for preparing the novel compounds of the invention in large scale. This novel method can also be used in large scale to obtain single enantiomers of omeprazole in neutral form.

The compounds according to the invention may be used for inhibiting gastric acid secretion in mammals and man. In a more general sense, the compounds of the invention may be used for the treatment of gastric acid-related diseases and gastrointestinal inflammatory diseases in mammals and man, such as gastric ulcer, duodenal ulcer, reflux esophagitis, and gastritis. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable e.g. in patients on NSAID therapy, in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration. The compound of the invention may also be used for treatment or prophylaxis of inflammatory conditions in mammals, including man, especially those involving lysozymal enzymes. Conditions that may be specifically mentioned for treatment are rheumatoid arthritis and gout. The compound of the invention may also be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections.

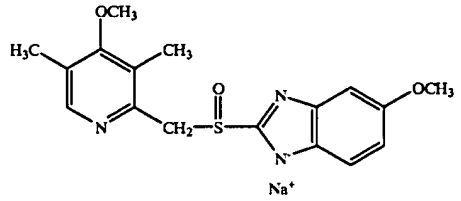
DETAILED DESCRIPTION OF THE INVENTION

The present invention refers to the new Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} and $N^+(R)_4$ salts of the single enantiomers of omeprazole, where R is an alkyl with 1–4 carbon atoms, i.e. Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} and $N^+(R)_4$ salts of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and (−)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, where R is an alkyl with 1–4 carbon atoms.

Particularly preferred salts according to the invention are the Na^+, Ca^{2+} and Mg^{2+} salts, i.e (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]1H-benzimidazole sodium salt, (−)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt, (−)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt, (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole calcium salt and (−)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole calcium salt.

Most preferred salts according to the invention are the optically pure Na^+ salts of omeprazole according to compounds Ia and Ib

(Ia, Ib)

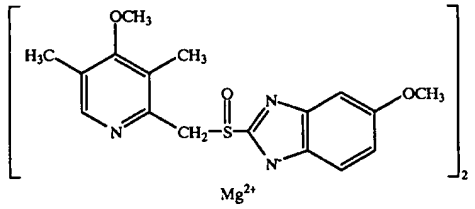


Ia (+)-enantiomer

Ib (−)-enantiomer

and the optically pure magnesium salts of omeprazole according to compounds IIa and IIb

(IIa, IIb)



IIa (+)-enantiomer

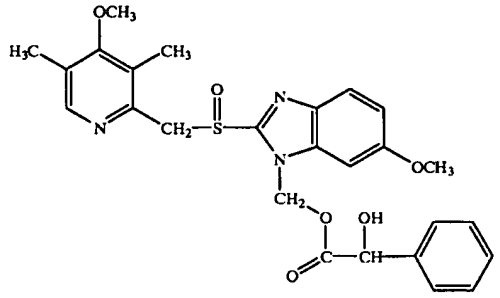
IIb (−)-enantiomer

With the expression "optically pure Na^+ salts of omeprazole" is meant the (+)-enantiomer of omeprazole Na-salt essentially free of the (−)-enantiomer of omeprazole Na-salt and the (−)-enantiomer essentially free of the (+)-enantiomer, respectively. Single enantiomers of omeprazole have hitherto only been obtained as syrups and not as crystalline products. The salts defined by the present invention are easy to obtain by means of the novel specific method according to one aspect of the invention of preparing the single enantiomers of omeprazole. In contrast to the neutral forms the salts can be obtained as crystalline products. Because it is possible to purify optically impure or partially pure salts of the enantiomers of omeprazole by crystallization, they can be obtained in very high optical purity, namely ≧99.8% enantiomeric excess (e.e.) even from an optically contaminated preparation. Moreover, the optically pure salts are stable resisting racemization both in neutral pH and basic pH, which is surprising since the known deprotonation at the carbon atom between the pyridine ring and the chiral sulfur atom was expected to cause racemization under alkaline conditions. This high stability against racemization makes it possible to use a single enantiomeric salt of the invention in therapy.

The specific method of preparation of the single enantiomers of omeprazole is a further aspect of the invention as mentioned above and it can be used to obtain the single enantiomers of omeprazole in neutral form as well as the salts thereof.

Yet a further aspect of the invention is the compound III, which is an intermediate used in the specific method of preparation.

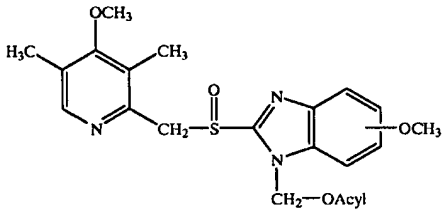
(III)



Preparation

The optically pure compounds of the invention, i.e. the single enantiomers, are prepared by separating the two stereoisomers of a diastereomeric mixture of the following type, 5- or 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-[acyloxymethyl]-1H-benzimidazole, formula IV

(IV)



wherein the methoxy substituent in the benzimidazole moiety is in position 5 or 6, and wherein the Acyl radical is as defined below, followed by a solvolysis of each separated diastereomer in an alkaline solution. The formed single enantiomers of omeprazole are then isolated by neutralizing aqueous solutions of the salts of the single enantiomers of omeprazole with a neutralizing agent which can be an acid or an ester such as methyl formate.

The Acyl moiety in the diastereomeric ester may be a chiral acyl group such as mandeloyl, and the asymmetric center in the chiral acyl group can have either R or S configuration.

The diastereomeric esters can be separated either by chromatography or fractional crystallization.

The solvolysis usually takes place together with a base in a protic solvent such as alcohols or water, but the acyl group may also be hydrolyzed off by a base in an aprotic solvent such as dimethylsulfoxide or dimethylformamide. The reacting base may be OH^- or R^1O^- where R^1 can be any alkyl or aryl group.

To obtain the optically pure Na^+ salts of the invention, i.e. the single enantiomers of omeprazole Na^+ salts, the resulting compound is treated with a base, such as NaOH, in an aqueous or nonaqueous medium, or with $NaOR^2$ wherein R^2 is an alkyl group containing 1–4 carbon atoms, or with $NaNH_2$. In addition, alkaline salts wherein the cation is Li^+ or K^+ may be prepared using lithium or potassium salts of the above mentioned bases. In order to obtain the crystalline form of the Na^+ salt, addition of NaOH in a non-aqueous medium such as a mixture of 2-butanone and toluene, is preferred.

To obtain the optically pure Mg^{2+} salts of the invention, optically pure enantiomeric Na^+ salts may be treated with an aqueous solution of an inorganic magnesium salt such as $MgCl_2$, whereupon the Mg^{2+} salts are precipitated. The optically pure Mg^{2+} salts may also be prepared by treating single enantiomers of omeprazole with a base, such as $Mg(OR^3)_2$, wherein R^3 is an alkyl group containing 1–4 carbon atoms, in a non-aqueous solvent such as alcohol (only for alcoholates), e.g. ROH, or in an ether such as tetrahydrofuran. In an analogous way, also alkaline salts wherein the cation is Ca^{2+} can be prepared, using an aqueous solution of an inorganic calcium salt such as $CaCl_2$.

Alkaline salts of the single enantiomers of the invention are, as mentioned above, beside the sodium salts (compounds Ia and Ib) and the magnesium salts (compounds Ia and IIb), exemplified by their salts with Li^+, K^+, Ca^{2+} and $N^+(R)_4$, where R is an alkyl with 1–4 C-atoms.

For clinical use the single enantiomers, i.e. the optically pure compounds, of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other modes of administrations. The pharmaceutical formulations contain the single enantiomers of the invention normally in combination with a pharmaceutically acceptable carrier. The carrier may be in form of a solid, semisolid or liquid diluent, or capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1–95% by weight of the preparation, between 0.2–20% by weight in preparations for parenteral use and between 1–50% by weight in preparations for oral administration.

In the preparation of pharmaceutical formulations in form of dosage units for oral administration the optically pure compound may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivates, gelatin or another suitable carrier, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethyleneglycol waxes. The mixture is then processed into granules or pressed into tablets. Granules and tablets may be coated with an enteric coating which protects the active compound from acid catalyzed degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers and the like, if preferred in combination with a suitable plasticizer. To the coating various dyes may be added in order to distinguish among tablets or granules with different amounts of the active compound present.

Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Soft gelatine capsules may also be enteric-coated as described above.

Hard gelatine capsules may contain granules or enteric-coated granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, amylopectin, cellulose derivates or gelatin. The capsules may be enteric-coated as described above.

Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules, or they may be prepared in the form of a ready-made micro enema, or they may be prepared in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparation for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and/or polyethylene glycol. If desired, such liquid preparations may contain coloring agents, flavoring agents, saccharine and carboxymethyl cellulose or other thickening agents. Liquid preparations for oral administration may also be prepared in the form of dry powder to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administrations may be prepared as solutions of the optically pure compounds of the invention in pharmaceutically acceptable solvents, preferably in a concentration from 0.1 to 10% by weight. These soultions may also contain stabilizing agents and/or buffering agents and may be manufactured in different unit dose ampoules or vials. Solutions for parenteral administration may also be prepared as dry preparations to be reconstituted with a suitable solvent extemporaneously before use.

The typical daily dose of the active compound will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 500 mg per day of active substance.

The invention is illustrated by the following examples using preferred procedures for the preparation of optically pure sodium salts and magnesium salts.

The processes described below for optically pure enantiomeric sodium salts of omeprazole result in change of directions from (−) to (+) optical rotation and, vice versa, from (+) to (−) optical rotation when preparing the sodium salt from the neutral form of omeprazole and again, when preparing the magnesium salt from the sodium salt of omeprazole.

EXAMPLE 1

Preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt

100 mg (0.3 mmol) of (−)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole (contaminated with 3% of the (+)-isomer) was dissolved in 1 ml of 2-butanone with stirring. 60 μl of an aqueous solution of 5.0 M sodium hydroxide and 2 ml of toluene were added. The resultant mixture was non-homogeneous. In order to obtain a clear solution, more 2-butanone was added (ca 1 ml) and the mixture was stirred at ambient temperature over night. The formed precipitate was filtered off and washed with ether. There was obtained 51 mg (46%) of the title compound as white crystals m.p. (decomposition) 246–248° C. The optical purity (e.e.) which was analyzed by chiral column chromatography was ≧99.8%. $[\alpha]_D^{20}$=+42,8° (concentration, c=0.5%, water).

NMR data are given below.

EXAMPLE 2

Preparation of (−)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt

100 mg-(0.3 mmol)of(+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole

(contaminated with 3% of the (−)-isomer) was dissolved in 1 ml of 2-butanone with stirring. 60 μl of an aqueous solution of 5.0 M sodium hydroxide and 2 ml of toluene were added. The resultant mixture was non-homogeneous. In order to obtain a clear solution, more 2-butanone was added (ca 1 ml) and the mixture was stirred at ambient temperature over night. The formed precipitate was filtered off and washed with ether. There was obtained 56 mg (51%) of the title compound as white crystals m.p. (decomposition) 247–249° C. The optical purity (e.e.) which was analyzed by chiral column chromatography was ≧99.8%. $[\alpha]_D^{20}$=−44.1° (c=0.5%, water).

NMR data are given below.

EXAMPLE 3

Preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

2.9 ml of a 0.1 M solution of NaOH was added to 0.10 g (0.29 mmol) (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole. To this mixture 2 ml methylene chloride was added, and after mixing in a separatory funnel the aqueous solution was separated off. A solution of 14 mg (0.145 mmol) $MgCl_2$ in water was added dropwise. The formed precipitate was isolated by centrifugation, and 52 mg (50%) of the product was isolated as an amorphous powder. The optical purity (e.e.) was 98%, and thus the same as the starting material. The optical purity was determined by chromatography on an analytical chiral column. $[\alpha]_D^{20}$=+101.2° (c=1%, methanol). The Mg content of the sample was found to be 3.0%, shown by atomic absorption spectroscopy.

EXAMPLE 4

Preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfiinyl]-1H-benzimidazole magnesium salt

(−)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt (0.500 g, 1.36 mmol) was dissolved in water (10 ml). To this mixture 10 ml of an aqueous solution of $MgCl_2 \times H_2O$ (138 mg, 0.68 mmol) was added dropwise and the formed precipitate was isolated by centrifugation. There was obtained 418 mg (86%) of the product as a white powder. The optical purity (ee) of the product was 99.8% which was the same as the optical purity of the starting material. The optical purity was determined by chromatography on an analytical chiral column. $[\alpha]_D^{20}$=+129.9° (c=1%, methanol).

EXAMPLE 5

Preparation of (−)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

(+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole sodium salt (0.165 g, 0.45 mmol) was dissolved in water (3 ml). To this mixture 2 ml of an aqueous solution of $MgCl_2 \times H_2O$ (46 mg, 0.23 mmol) was added dropwise and the formed precipitate was isolated by centrifugation. There was obtained 85 mg (51%) of the product as a white powder. The optical purity (ee) of the product was 99.9% which was the same or better as the optical purity of the starting material. The optical purity was determined by chromatography on an analytical chiral column. $[\alpha]_D^{20}$=−128.2° (c=1%, methanol).

TABLE 1

Ex.	Solvent	NMR data δ ppm
1.	DMSO-d_6 500 MHz	2.20 (s, 3H), 2.22 (s, 3H), 3.69 (s, 3H), 3.72 (s, 3H), 4.37 (d, 1H), 4.75 (d, 1H), 6.54 (dd, 1H), 6.96 (d, 1H), 7.30 (d, 1H), 8.21 (s, 1H).
2.	DMSO-d_6 500 MHz	2.20 (s, 3H), 2.22 (s, 3H), 3.69 (s, 3H), 3.72 (s, 3H), 4.38 (d, 1H), 4.73 (d, 1H), 6.54 (dd, 1H), 6.96 (d, 1H), 7.31 (d, 1H), 8.21 (s, 1H).

A preferred method for preparing optically pure omeprazole enantiomer crystal salts of magnesium is described in Examples 6 and 7.

EXAMPLE 6

Enhancement of the optical purity by preparing the magnesium salt of (−)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole in nonagueous solution followed by crystallization of said salt

Magnesium (0.11 g, 4.5 mmol) was dissolved and reacted with methanol (50 ml) at 40° C. with a catalytic amount of methylene chloride. The reaction was run under nitrogen and was finished after five hours. At room temperature a mixture of the two enantiomers [90%(−)-isomer and 10%(+)-isomer] of 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole (2.84 g, 8.2 mmol) was added to the magnesium methoxide solution. The mixture was stirred for 12 hours whereupon a small amount of water (0.1 ml) was added in order to precipitate inorganic magnesium salts. After 30 minutes stirring, these inorganic salts were filtered off and the solution was concentrated on a rotavapor. The residue was now a concentrated methanolic solution of the enantiomeric mixture (i.e. the title compound contaminated with the (+)-isomer), with an optical purity (enantiomeric excess, e.e.) of 80%. This mixture was diluted with acetone (100 ml) and after stirring at room temperature for 15 minutes, a white precipitate was obtained. Additional stirring for 15 mintues and thereafter filtration afforded 1.3 g (50%) of the title compound as white crystals. Chiral analyses of the crystals and mother liquor were performed by chromatography on an analytical chiral column. The optical purity of the crystals and mother liquor was found to be 98.4 e.e. and 64.4% e.e., respectively. Thus, the optical purity (e.e.) has been enhanced from 80% to 98.4% simply by crystallizing the Mg-salt from a mixture of acetone and methanol. The product was crystalline as shown by powder X-ray diffraction and the magnesium content was 3.44% as shown by atomic absorption spectroscopy. $[\alpha]_D^{2}$=−131.5° (c=0.5%, methanol).

EXAMPLE 7

Enhancement of the optical purity by preparing the magnesium salt of (+)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole in nonaqueous solution followed by crystallization of said salt

Magnesium (0.11 g, 4.5 mmol) was dissolved and reacted with methanol (50 ml) at 40° C. with a catalytic amount of methylene chloride. The reaction was run under nitrogen and was finished after five hours. At room temperature a mixture of the two enantiomers [90%(+)-isomer and 10%(−)-isomer]

of 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole (2.84 g, 8.2 mmol) was added to the magnesium methoxide solution. The mixture was stirred for 12 hours whereupon a small amount of water (0.1 ml) was added in order to precipitate inorganic magnesium salts. After 30 minutes stirring, these inorganic salts were filtered off and the solution was concentrated on a rotavapor. The residue was now a concentrated methanolic solution of the enantiomeric mixture (i.e. the title compound contaminated with the (−)-isomer), with an optical purity (e.e.) of 80%. This mixture was diluted with acetone (100 ml) and after stirring at room temperature for one hour, a white precipitate was obtained. Additonal stirring for 30 minutes and thereafter filtration afforded 0.35 g of the title compound as white crystals. Additional stirring of the mother liquor for 24 hours at room temperature afforded another 1.0 g (total yield=52%). Chiral analyses of the crystals and the second mother liquor were performed by chromatography on an analytical chiral column. The optical purity of the two crystal fractions was 98.8% e.e. and 99.5% e.e., respectively. The optical purity of the mother liquor was found to be 57% e.e. Thus, the optical purity (e.e.) has been enhanced from 80% to approximately 99% simply by crystallizing the Mg-salt from a mixture of acetone and methanol. The first precipitation was crystalline as shown by powder X-ray diffraction and the magnesium content of the same fraction was 3.49% as shown by atomic absorption spectroscopy. $[\alpha]_D^{20}$=+135.6° (c=0.5%, methanol).

The crystalline salt according to Example 6 is most preferred.

Preparation of the synthetic intermediates according to the invention is described in the following examples.

EXAMPLE 8

Preparation of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole

A solution of 3.4 g sodium hydroxide in 40 ml water was added to a mixture of 14.4 g (42 mmol) tetrabutylammonium hydrogen sulfate and 6.4 g (42 mmol) (R)(−)-mandelic acid. The mixture was extracted with 400 ml chloroform. After separation, the organic extract was heated to reflux with 16.6 g (42 mmol) of the racemate of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1-[chloromethyl]-1H-benzimidazole. Evaporation of the solvent was followed by dilution with 100 ml dichloromethane and 700 ml ethyl acetate. The mixture was washed with 3x200 ml water and the organic solution was dried over $MgSO_4$ and then evaporated. The crude material was purified by recrystallization from 100 ml acetonitrile, giving 8.1 g of the title compound (38%) as a diastereomeric mixture.

NMR data are given below.

EXAMPLE 9

Separation of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1[(R) mandeloyloxymethyl]-1H-benzimidazole

The diastereomers of the title compound in Example 8 were separated using reversed phase chromatography (HPLC). Approximately 300 mg of the diastereomeric mixture was dissolved in 10 ml hot acetonitrile which was diluted with 10 ml of a mixture of aqueous 0.1 M ammoniumacetate and acetonitrile (70/30). The solution was injected to the column and the compounds were eluted with a mixture of aqueous 0.1 M ammoniumacetate and acetonitrile (70/30). The more hydrophilic isomer was easier to obtain pure than the less hydrophilic one. The work up procedure for the fraction which contained pure isomer was as follows; extraction with dichloromethane, washing the organic solution with aqueous 5% sodium hydrogen carbonate solution, drying over Na_2SO_4 and evaporation of the solvent on a rotavapor (at the end of the evaporation the removal of acetonitrile was facilitated by adding more dichloromethane). Using 1.2 g of the diastereomeric mixture with the above mentioned technique, the more hydrophilic isomer, 410 mg, was obtained in a pure state as a colorless syrup.

NMR data are given below.

EXAMPLE 10

Preparation of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole

The product was obtained from 8.1 g (202 mmol) sodium hydroxide in 100 ml water, 34.4 g (101 mmol) tetrabutylammonium hydrogen sulfate, 15.4 g (101 mmol) (S)-(+)-mandelic acid and 39.9 g (101 mmol) of the racemate of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]-sulfinyl]-1 -[chloromethyl]-1H-benzimidazole using the same procedure as in Example 8. Recrystallization from 100 ml acetonitrile yielded 21.3 g, i.e. 41% of the title compound as a diastereomeric mixture.

NMR data are given below.

EXAMPLE 11

Separation of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole

The diastereomers of the title compound in Example 10 were separated using reversed phase chromatography (HPLC) in the same way as in Example 7, but using the diasteromeric mixture of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloloxymethyl]-1H-benzimidazole instead of the (R)-mandelic ester used in Example 9. Using 2.1 g of the diastereomeric mixture, the more hydrophilic isomer, 760 mg, was obtained in a pure state as a colorless syrup.

NMR data are given below.

EXAMPLE 12

Preparation of (−)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole

0.23 g (0.45 mmol) of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole was dissolved in 15 ml methanol. A solution of 36 mg (0.9 mmol) sodium hydroxide in 0.45 ml water was added, and after 10 minutes the mixture was evaporated on a rotavapor. The residue was partitioned between 15 ml water and 15 ml dichloromethane. The organic solution was extracted with 15 ml water and to the combined aqueous solutions was added 85 μl (1.4 mmol) methyl formate. After 15 minutes the mixture was extracted with 3x10 ml dichloromethane. The organic solution was dried over Na_2SO_4 and

then evaporated. There was obtained 0.12 g (77%) of the title compound as a colorless syrup. The optical purity (e.e.) which was analyzed by chiral column chromatography was 94%. $[\alpha]_D^{20}=-155°$ (c=0.5%, chloroform).

NMR data are given below

EXAMPLE 13

Preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole

0.76 g (1.5 mmol) of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole was dissolved in 50 ml methanol. A solution of 0.12 mg (3.0 mmol) sodium hydroxide in 1.5 ml water was added, and after 10 minutes the mixture was evaporated on a rotavapor. The residue was partitioned between 25 ml water and 25 ml dichloromethane. The organic solution was extracted with 25 ml water and to the combined aqueous solutions was added 200 μl (3.2 mmol) methyl formate. After 15 minutes the mixture was extracted with 3×25 ml dichloromethane. The organic solution was dried over Na_2SO_4 and then evaporated. There was obtained 0.42 g (81%) of the title compound as a colorless syrup. The optical purity (e.e.) which was analyzed by chiral column chromatography was 98%. $[\alpha]_D^{20}=+157°$ (c=0.5%, chloroform).

NMR data are given below

TABLE 2

Ex.	Solvent	NMR data δ ppm
8.	$CDCl_3$ 500 MHz	2.18 (s, 3H), 2.20 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 4.80 (d, m), 4.88 (d, 1H), 5.0 (m, 2H), 5.34 (s, 2H), 6.43 (d, 1H), 6.54 (d, 1H), 6.6–6.7 (m, 2H), 6.96 (d, 1H), 6.95–6.98 (m, 2H), 7.01 (d, 1H), 7.2–7.3 (m, 6H), 7.37 (m, 2H), 7.44 (m, 2H), 7.58 (d, 1H), 7.62 (d, 1H), 7.95 (s, 1H), 7.97 (s, 1H).
9.	$CDCl_3$ 500 MHz	2.20 (s, 3H), 2.36 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.80 (d, 1H), 5.00 (d, 1H), 5.35 (d, 1H), 6.43 (d, 1H), 6.63 (d, 1H), 6.90 (d, 1H), 6.97 (dd, 1H), 7.2–7.3 (m, 3H), 7.37 (m, 2H), 7.62 (d, 1H), 7.97 (s, 1H).
10.	$CDCl_3$ 500 MHz	2.19 (s, 3H), 2.20 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 3.83 (s, 3H), 3.87 (s, 3H), 4.80 (d, 1H), 4.88 (d, 1H), 5.0 (m, 2H), 5.34 (s, 2H), 6.43 (d, 1H), 6.54 (d, 1H), 6.6–6.7 (m, 2H), 6.90 (d, 1H), 6.96–6.98 (m, 2H), 7.01 (d, 1H), 7.2–7.3 (m, 6H), 7.37 (m, 2H), 7.44 (m, 2H), 7.58 (d, 1H), 7.62 (d, 1H), 7.95 (s, 1H), 7.97 (s, 1H).
11.	$CDCl_3$ 500 MHz	2.20 (s, 3H), 2.36 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.80 (d, 1H), 5.00 (d, 1H), 5.35 (d, 1H), 6.43 (d, 1H), 6.63 (d, 1H), 6.90 (d, 1H), 6.97 (dd, 1H), 7.2–7.3 (m, 3H), 7.37 (m, 2H), 7.62 (d, 1H), 7.97 (s, 1H).
12.	$CDCl_3$ 300 MHz	2.18, (s, 3H), 2.22 (s, 3H), 3.68 (s, 3H), 3.83 (s, 3H), 4.77(m, 2H), 6.93 (dd, 1H), ~7.0 (1), 1H), ~7.5 (b, 1H), 8.19 (s, 1H).
13.	$CDCl_3$	2.21 (s, 3H), 2.23 (s, 3H), 3.69 (s, 3H), 3.84 (s, 3H), 4.76 (m, 2H), 6.94 (dd, 1H), 7.0 (1,, 1H), ~7.5 (1), 1H), 8.20 (s, 1H).

Pharmaceutical preparations containing the compounds of the invention as active ingredient are illustrated in the following formulations.

Syrup

A syrup containing 1% (weight per volume) of active substance was prepared from the following ingredients:

Compound according to Example 1	1.0 g
Sugar, powder	30.0 g
Saccharine	0.6 g
Glycerol	5.0 g
Flavoring agent	0.05 g
Ethanol 96%	5.0 g
Distilled water q.s. to a final volume of	100 ml

Sugar and saccharine were dissolved in 60 g of warm water. After cooling the active compound was added to the sugar solution and glycerol and a solution of flavoring agents dissolved in ethanol were added. The mixture was diluted with water to a final volume of 100 ml.

Enteric-coated tablets

An enteric coated tablet containing 50 mg of active compound was prepared from the following ingredients:

I	Compound according to Example 6 as Mg salt	500 g
	Lactose	700 g
	Methyl cellulose	6 g
	Polyvinylpyrrolidone cross-linked	50 g
	Magnesium stearate	15 g
	Sodium carbonate	6 g
	Distilled water	q.s.
II	Cellulose acetate phthalate	200 g
	Cetyl alcohol	15 g
	Isopropanol	2000 g
	Methylene chloride	2000 g

I Compound according to Example 6, powder, was mixed with lactose and granulated with a water solution of methyl

cellulose and sodium carbonate. The wet mass was forced through a sieve and the granulate dried in an oven. After drying the granulate was mixed with polyvinylpyrrolidone and magnesium stearate. The dry mixture was pressed into tablet cores (10 000 tablets), each tablet containing 50 mg of active substance, in a tabletting machine using 7 mm diameter punches.

II A solution of cellulose acetate phthalate and cetyl alcohol in isopropanol/methylene chloride was sprayed onto the tablets I in an Accela Cota^R, Manesty coating equipment. A final tablet weight of 110 mg was obtained.

Solution for intravenous administration

A parenteral formulation for intravenous use, containing 4 mg of active compound per ml, was prepared from the following ingredients:

Compound according to Example 2	4 g
Sterile water to a final volume of	1000 ml

The active compound was dissolved in water to a final volume of 1000 ml. The solution was filtered through a 0.22 μm filter and immediately dispensed into 10 ml sterile ampoules. The ampoules were sealed.

Capsules

Capsules containing 30 mg of active compound were prepared from the following ingredients:

Compound according to Example 6	300 g
Lactose	700 g
Microcrystalline cellulose	40 g
Hydroxypropyl cellulose low-substituted	62 g
Disodium hydrogen phosphate	2 g
Purified water	q.s.

The active compound was mixed with the dry ingredients and granulated with a solution of disodium hydrogen phosphate. The wet mass was forced through an extruder and spheronized and dried in a fluidized bed dryer.

500 g of the pellets above were first coated with a solution of hydroxypropyl methylcellulose, 30 g, in water, 750 g, using a fluidized bed coater. After drying, the pellets were coated with a second coating as given below:

Coating solution:

Hydroxypropyl methylcellulose phthalate	70 g
Cetyl alcohol	4 g
Acetone	200 g
Ethanol	600 g

The final coated pellets were filled into capsules.

Suppositories

Suppositories were prepared from the following ingredients using a welding procedure. Each suppository contained 40 mg of active compound.

Compound according to Example 1	4 g
Witepsol H-15	180 g

The active compound was homogenously mixed with Witepsol H-15 at a temperature of 41° C. The molten mass was volume filled into pre-fabricated suppository packages to a net weight of 1.84 g. After cooling the packages were heat sealed. Each suppository contained 40 mg of active compound.

Stability towards racemization at different pH values

The stability of the optically pure compounds of the invention against racemization has been measured at low concentrations in a refrigerator in aqueous buffer solutions at pH 8, 9.3, 10 and 11.2. The stereochemical stability was measured by comparing the optical purity for the (−)-isomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole in buffer solution immediately after dissolving and after several days. The measurement was performed by chromatography on an analytical chiral column. The surprising high stereochemical stability in alkaline conditions for the compounds of invention is exemplified by the fact that no racemization for the test compound was obtained at pH 11.2 even after 21 days. At pH 8, 9.3 and 10, the chemical degradation of the compound is more apparent which makes the racemization measurement more difficult to perform, however at none of these pH values a detectable racemization was obtained after 16 days.

In another racemization experiment with the optically pure compounds of the invention, an aqueous phosphate buffer solution (pH=11) of the (+)-isomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H benzimidazole sodium salt ($c=10^{-5}M$) was warmed for 26 hours at 37° C. without any racemization at all being observed.

What is claimed is:

1. A pharmaceutical formulation for parenteral administration comprising an optically pure solid state Na^+salt of the (−)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole as active ingredient, and a pharmaceutically acceptable carrier.

2. A pharmaceutical formulation for parenteral administration comprising an injection solution comprising an optically pure solid state Na^+ salt of the (−)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole as active ingredient, and a pharmaceutically acceptable carrier in the form of a pharmaceutically acceptable solvent having a volume sufficient to effect a solution having a concentration of 0.1 to 10% by weight of the active ingredient.

3. The pharmaceutical formulation according to claim 1 or 2, wherein the solid state salt is in substantially crystalline form.

4. The pharmaceutical formulation according to claim 1 or 2, further comprising a stabilizing agent, a buffering agent or a mixture thereof.

5. The pharmaceutical formulation for parenteral administration according to claim 1, comprising an injectable solution.

6. A method of inhibiting gastric acid secretion comprising the parenteral administration to a mammal including man in need of such treatment of a pharmaceutical formulation comprising a therapeutically effective amount of an optically pure solid state Na^+ salt of the (−)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole and a pharmaceutically acceptable carrier.

7. A method for the treatment of gastrointestinal inflammatory disease comprising the parenteral administration to a mammal including man in need of such treatment of a pharmaceutical formulation comprising a therapeutically effective amount of an optically pure solid state Na^+ salt of the (−)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, and a pharmaceutically acceptable carrier.

8. The method according to claim 7, wherein a solution with the solvent carrier is prepared immediately before the administration.

9. The method according to claim 6 or 7, wherein the pharmaceutically acceptable carrier is in the form of a solvent.

10. The method of claim 7, wherein the solvent has a volume effecting a solution of a concentration of 0.1–10% by weight of the active ingredient.

11. A method of inhibiting gastric acid secretion comprising injecting a mammal including man in need of such treatment with a solution of an optically pure solid state Na^+ salt of the (–)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and a pharmaceutically acceptable solvent having a volume sufficient to effect a solution having a concentration of 0.1 to 10% by weight of the active ingredient.

12. A method for the treatment of gastrointestinal inflammatory disease comprising injecting a mammal including man in need of such treatment with a solution of an optically pure solid state Na^+ salt of the (–)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and a pharmaceutically acceptable solvent having a volume sufficient to effect a solution having a concentration of 0.1 to 10% by weight of the active ingredient.

* * * * *

EXHIBIT B

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,143,771
DATED : November 7, 2000
INVENTOR(S) : Lindberg, et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In claim 8, col. 15, line 1, delete "claim 7" and substitute therefor -- claim 9 --.

In claim 10, col. 15, line 7, delete "claim 7" and substitute therefor -- claim 9 --.

Signed and Sealed this

Eighth Day of May, 2001

Attest:

Nicholas P. Godici

NICHOLAS P. GODICI

Attesting Officer

Acting Director of the United States Patent and Trademark Office

EXHIBIT C

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
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WHITE & CASE LLP
PATENT DEPARTMENT
1155 AVENUE OF THE AMERICAS
NEW YORK NY 10036

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the U.S. Patent and Trademark Office. If the maintenance fee and any necessary surcharge have been timely paid for the patent listed below, the notation "PAID" will appear in the "STAT" column.

If the statement of small entity status is defective the reason will be indicated below in the "Small Entity" status column. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

PATENT NUMBER	FEE AMT	SUR CHARGE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	STAT	ATTY DKT NUMBER
6,143,771	**$910.00**	**$0.00**	**09/419,456**	**11/07/00**	**10/15/99**	**04**	**NO**	**PAID**	**1103326-0072**

Direct any questions about this notice to:
Mail Stop M Correspondence
Director of the U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

EXHIBIT D

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09/419,456 and of U.S. Patent No. 5,714,504 by Assignment
7438, Frame 0120.

Astra Aktiebolag, by its undersigned agent, sta
have been reviewed and certifies that, to the best of its knowle
Serial No. 09/419,456 and U.S. Patent No. 5,714,504 is in As
claimed in U.S. Serial No. 09/419,456 and U.S. Patent No. 5,
Astra Aktiebolag at the time the later invention was made.

Astra Aktiebolag hereby disclaims, except as p
of the statutory term of any patent granted on the above-ident
extend beyond the expiration date of the full statutory term as
and 173 of prior U.S. Patent No. 5,714,504. Astra Aktiebola
granted on the above-identified application shall be enforceabl
and U.S. Patent No. 5,714,504 are commonly owned. This a
granted on the above-identified application and is binding upo
assigns.

In making the above disclaimer, petitioner doe
any patent granted on the instant application that would exten
statutory term as defined in 35 U.S.C. §§154 to 156 and 173
event that the prior patent: expires for failure to pay a mainte
found invalid by a court of competent jurisdiction, is statutori
disclaimed under 37 C.F.R. §1.321, has all claims canceled by
reissued or is in any manner terminated prior to the expiration
presently shortened by any terminal disclaimer.

1103326-0072

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	: Lindberg et al.
Serial No.	: 09/419,456
Filed	: October 12, 1999
For	: NEW COMPOUNDS
Examiner	:
Group Art Unit	:

I hereby certify that this paper is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents Washington, D.C. 20231.

John M. Genova 32,224
Attorney Name PTO Reg. No.

John M Genova 11/12/99
Signature Date of Signature

Assistant Commissioner for Patents
Washington, D.C. 20231

TERMINAL DISCLAIMER

Sir:

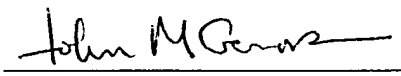
Astra Aktiebolag, a corporation created and existing under the laws of Sweden, and having a business address at S-151 85 Södertälje, Sweden, hereby through its undersigned agent, who is empowered to act on behalf of Astra Aktiebolag, represents that Astra Aktiebolag is the owner of the entire right, title and interest of the above-identified patent application Serial No.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

In connection with the filing of this Terminal Disclaimer, the Commissioner is hereby authorized to charge the fee of $110.00 as required by 37 C.F.R. § 1.20(d) to Deposit Account No. 23-1703.

Dated: November 12, 1999

Astra Aktiebolag



John M. Genova
Reg. No. 32,224
Attorney for Applicants

White & Case LLP
Patent Department
1155 Avenue of the Americas
New York, NY 10036-2787
(212) 819-8200

Date 11 / 12 / 99
Mo Day Yr

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Atty. Docket 1108826-0072

Serial No. 09/419,456

Sir:

Kindly acknowledge receipt of the accompanying:

- ☐ Maintenance Fee Transmittal and check for $ _____
- ☒ ~~Response to Official Action~~: Letter + Declaration of Tommy Andersson.
- ☐ Check for $ _____ (claims fee)
- ☐ Petition under 37 CFR 1.136 and Check for $ _____
- ☐ Notice of Appeal and Check for $ _____
- ☒ Information Disclosure Statement, PTO - 1449 and copies of ___ references
- ☐ Claim priority and certified copies of _____ priority applications
- ☐ Issue fee transmittal and Check for $ _____
- ☒ Other (specify) Terminal Disclaimer.

by placing your receiving date stamp hereon and mailing or returning to deliverer.

Atty. J. Genova Due Date ___ / ___ / ___
Mo Day Yr

37 CFR 1.8 ☒
37 CFR 1.10 ☐
By Hand

EXHIBIT E

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	: Lindberg et al.
Serial No.	: 09/419,456
Filed	: October 15, 1999
For	: NEW COMPOUNDS
Examiner	: J. Fan
Group Art Unit	: 1612

CERTIFICATE OF TRANSMISSION UNDER 37 C.F.R. 1.8

I hereby certify that this paper is being facsimile transmitted to the U.S. Patent and Trademark Office on April 28, 2000 at the facsimile number 703-308-4556.

John M. Genova — 32,224
Attorney Name — PTO Reg. No.

John M Genova — 28 April 2000
Signature — Date of Signature

Assistant Commissioner for Patents
Washington, D.C. 20231

ATTENTION: Examiner Jane Fan
FACSIMILE NO: 703-308-4556
DATE: April 28, 2000
PAGES: 3

TERMINAL DISCLAIMER

Sir:

Astra Aktiebolag, a corporation created and existing under the laws of Sweden, and having a business address at S-151 85 Södertälje, Sweden, hereby through its undersigned agent, who is empowered to act on behalf of Astra Aktiebolag, represents that Astra Aktiebolag is

the owner of the entire right, title and interest of the above-identified patent application Serial No. 09/419,456 and of U.S. Patent No. 5,877,192 by Assignments recorded on April 17, 1995, Reel 7438, Frame 0120 and on November 14, 1997, Reel 8814, Frame 0101, respectively.

Astra Aktiebolag by its undersigned agent states that all evidentiary documents have been reviewed and certifies that, to the best of its knowledge and belief, title to Application Serial No. 09/419,456 and U.S. Patent No. 5,877,192 is in Astra Aktiebolag. The inventions claimed in U.S. Serial No. 09/419,456 and U.S. Patent No. 5,877,192 were commonly owned by assignee at the time the later invention was made.

Astra Aktiebolag hereby disclaims, except as provided below, the terminal portion of the statutory term of any patent granted on the above-identified application which would extend beyond the expiration date of the full statutory term as defined in 35 U.S.C. § 154 to 156 and 173, of prior U.S. Patent No. 5,877,192. Astra Aktiebolag hereby agrees that any patent so granted on the above-identified application shall be enforceable only for and during such period it, and U.S. Patent No. 5,877,192 are commonly owned. This agreement is to run with any patent granted on the above-identified application and is upon the grantee, its successors or assigns.

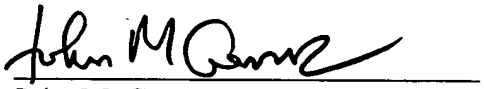
In making the above disclaimer, petitioner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 to 156 and 173 of U.S. Patent No. 5,877,192, in the event that the prior patent later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

The Assistant Commissioner is authorized to charge Deposit Account No. 23-1703 in the amount of One Hundred and Ten Dollars ($110.00) pursuant to 37 C.F.R. §1.20(d) and any additional fee required in connection with this communication.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: April 28, 2000

Astra Aktiebolag



John M. Genova
Reg. No. 32,224
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1103326-0072

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	: Lindberg et al.
Serial No.	: 09/419,456
Filed	: October 15, 1999
For	: NEW COMPOUNDS
Examiner	: J. Fan
Group Art Unit	: 1612

CERTIFICATE OF TRANSMISSION
UNDER 37 C.F.R. 1.8

I hereby certify that this paper is being facsimile transmitted to the U.S. Patent and Trademark Office on April 28, 2000 at the facsimile number 703-308-4556.

John M. Genova — 32,224
Attorney Name — PTO Reg. No.

John M Genova — 28 April 2000
Signature — Date of Signature

Assistant Commissioner for Patents
Washington, D.C. 20231

ATTENTION: Examiner Jane Fan

FACSIMILE NO: 703-308-4556

DATE: April 28, 2000

PAGES: **3**

TERMINAL DISCLAIMER

Sir:

EXHIBIT F

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EXHIBIT F

PATENT CLAIM COVERAGE OF APPROVED PRODUCT

Applicable Claims of U.S. Patent No. 6,143,771	Manner in Which Each Claim Reads on Approved Product (Nexium® I.V.) or Method of Using the Approved Product
1. A pharmaceutical formulation for parenteral administration comprising an optically pure solid state Na^+ salt of the (-)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole as active ingredient, and a pharmaceutically acceptable carrier.	Nexium® I.V. for Injection (esomeprazole sodium for injection 20 and 40 mg) ("Nexium® I.V.") is supplied as a freeze-dried powder that is reconstituted into a pharmaceutical formulation for parenteral administration by intravenous injection or intravenous infusion. It contains as its active ingredient, esomeprazole sodium, which is the sodium salt of esomeprazole ((S)-5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1 H-benzimidazole). Esomeprazole is the (-)-enantiomer of omeprazole, which itself is 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1 H-benzimidazole. The approved labeling information for Nexium® I.V. requires reconstitution with 0.9% Sodium Chloride Injection, USP; Lactated Ringer's Injection, USP; or 5% Dextrose Injection, USP as pharmaceutically acceptable carriers. Nexium® I.V. is therefore within the scope of claim 1.
2. A pharmaceutical formulation for parenteral administration comprising an injection solution comprising an optically pure solid state Na^+ salt of the (-)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole as active ingredient, and a pharmaceutically acceptable carrier in the form of a pharmaceutically acceptable solvent having a volume sufficient to effect a solution having a concentration of 0.1 to 10% by weight of the active ingredient.	The approved labeling information for Nexium® I.V. requires the freeze-dried powder containing the active ingredient to be reconstituted with 5 mL of 0.9% Sodium Chloride Injection, USP for administration by intravenous injection. The volume of the diluent effects an injection solution having a concentration of 0.4% by weight of the active ingredient for the 20 mg dose and a concentration of 0.8% by weight of the active ingredient for the 40 mg dose. Nexium® I.V. is therefore within the scope of claim 2.
4. The pharmaceutical formulation according to claim 1 or 2, further comprising a stabilizing agent, a buffering agent or a mixture thereof.	As supplied, Nexium® I.V. for Injection comprises sodium hydroxide q.s. as a stabilizing agent, a buffering agent or a mixture thereof. Nexium® I.V. is therefore within the scope of claim 4.
5. The pharmaceutical formulation for parenteral administration according to claim 1, comprising an injectable solution.	The approved labeling information for Nexium® I.V. requires that the freeze-dried powder containing the active ingredient be reconstituted as a solution for administration by intravenous injection or intravenous

Applicable Claims of U.S. Patent No. 6,143,771	Manner in Which Each Claim Reads on Approved Product (Nexium® I.V.) or Method of Using the Approved Product
	infusion. Nexium® I.V. is therefore within the scope of within the scope of claim 5.
6. A method of inhibiting gastric acid secretion comprising the parenteral administration to a mammal including man in need of such treatment of a pharmaceutical formulation comprising a therapeutically effective amount of an optically pure solid state Na^+ salt of the (-)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzi-midazole and a pharmaceutically acceptable carrier.	The sodium salt of esomeprazole inhibits gastric acid secretion in humans. Nexium® I.V. is approved for the short-term intravenous treatment of GERD patients with a history of erosive esophagitis when oral therapy is not possible or appropriate. The method of treating GERD by inhibiting gastric acid secretion via administration of Nexium® I.V. is therefore within the scope of claim 6.
7. A method for the treatment of gastrointestinal inflammatory disease comprising the parenteral administration to a mammal including man in need of such treatment of a pharmaceutical formulation comprising a therapeutically effective amount of an optically pure solid state Na^+ salt of the (-)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzi- midazole, and a pharmaceutically acceptable carrier.	Nexium® I.V. is approved for the short-term intravenous treatment of GERD patients with a history of erosive esophagitis, which can be a gastrointestinal inflammatory disease. The method of treatment of such patients by administration of Nexium® I.V. is therefore within the scope of claim 7.
8. The method according to claim 7, wherein a solution with the solvent carrier is prepared immediately before the administration.	The approved labeling information for Nexium® I.V. requires administration of the solution containing the active ingredient and solvent carrier within 12 hours for administration by intravenous injection after reconstitution with 0.9% Sodium Chloride Injection, USP and for administration by intravenous infusion after reconstitution with 0.9% Sodium Chloride Injection, USP or Lactated Ringer's Injection, USP; or within 6 hours for administration by intravenous infusion after reconstitution with 5% Dextrose Injection, USP. The solution with the solvent carrier therefore may be prepared immediately before the administration. The method of treatment of GERD by administration of Nexium® I.V. is therefore within the scope of claim 8.
9. The method according to claim 6 or 7, wherein the pharmaceutically acceptable carrier is in the form of a solvent.	The approved labeling for Nexium® I.V. requires reconstitution of the freeze-dried powder containing esomeprazole sodium with any of the following

Applicable Claims of U.S. Patent No. 6,143,771	Manner in Which Each Claim Reads on Approved Product (Nexium® I.V.) or Method of Using the Approved Product
	solvents prior to intravenous administration: 0.9% Sodium Chloride Injection, USP; Lactated Ringer's Injection, USP; or 5% Dextrose Injection, USP. The method of treatment of GERD by administration of Nexium® I.V. is therefore within the scope of claim 9.
10. The method of claim 7, wherein the solvent has a volume effecting a solution of a concentration of 0.1-10% by weight of the active ingredient.	The approved labeling information for Nexium® I.V. requires the freeze-dried powder containing the active ingredient to be reconstituted with 5 mL of any of specified solvents for administration by intravenous injection or infusion. The volume of the diluent effects a solution having a concentration of 0.4 % by weight of the active ingredient for the 20 mg dose and a concentration of 0.8 % by weight of the active ingredient for the 40 mg dose. The method of treatment of GERD by administration of Nexium® I.V. is therefore within the scope of claim 10.
11. A method of inhibiting gastric acid secretion comprising injecting a mammal including man in need of such treatment with a solution of an optically pure solid state Na^+ salt of the (-)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and a pharmaceutically acceptable solvent having a volume sufficient to effect a solution having a concentration of 0.1 to 10% by weight of the active ingredient.	The sodium salt of esomeprazole inhibits gastric acid secretion in humans. The approved labeling information for Nexium® I.V. requires the freeze-dried powder containing the active ingredient to be reconstituted with 5 mL of 0.9% Sodium Chloride Injection, USP for administration by intravenous injection. The volume of the diluent effects a solution having a concentration of 0.4 % by weight of the active ingredient for the 20 mg dose and a concentration of 0.8 % by weight of the active ingredient for the 40 mg dose. The method of treatment of GERD by administration of Nexium® I.V. is therefore within the scope of claim 11.
12. A method for the treatment of gastrointestinal inflammatory disease comprising injecting a mammal including man in need of such treatment with a solution of an optically pure solid state Na^+ salt of the (-)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and a pharmaceutically acceptable solvent having a volume sufficient to effect a solution having a concentration of 0.1 to 10% by weight of the active ingredient.	Nexium® I.V. is approved for the short-term intravenous treatment of GERD patients with a history of erosive esophagitis, which can be a gastrointestinal inflammatory disease. The approved labeling information for Nexium® I.V. requires the freeze-dried powder containing the active ingredient to be reconstituted with 5 mL of 0.9% Sodium Chloride Injection, USP for administration by intravenous injection. The volume of the diluent effects a solution having a concentration of 0.4 % by weight of the active ingredient for the 20 mg dose and a concentration of 0.8 % by weight of the active ingredient for the 40 mg dose. The method of treatment of GERD by administration of Nexium® I.V. is therefore within the scope of claim 12.

EXHIBIT G

CHRONOLOGY OF SIGNIFICANT ACTIVITIES
IND 64,865 and NDA 21-689

Application No.	Date	Description
IND 53,733	Oct. 25, 2001	Submitted a background package for a Type B meeting to discuss the proposed clinical and non-clinical program for an IV formulation of Nexium.
IND 53,733	Dec. 6, 2001	Type B FDA meeting held.
IND 53,733	Dec. 14, 2001	AstraZeneca submitted the meeting minutes of the December 6 FDA meeting.
IND 53,733	April 11, 2002	FDA provided their December 6 meeting minutes.
IND 64,865	May 22, 2002	Submitted Original IND.
IND 64,865	July 10, 2002	Submitted a background package for a pre-NDA CMC meeting.
IND 64,865	July 15, 2002	Submitted Amendment 1 to protocols SH-NEP-0011, SH-NEP-0012, D9615C00013, and D9615C00014 that were submitted in the original IND.
IND 64,865	July 17, 2002	Submitted correction to CMC background package.
IND 64,865	Aug. 8, 2002	The August 14, 2002 pre-NDA CMC meeting was canceled August 5. The FDA provided written response to questions submitted in the background package.
IND 64,865	Oct. 10, 2002	Submitted a copy of AstraZeneca's meeting minutes of the teleconference held on Sept. 12 to discuss various Nexium IV CMC related issues in connection with the NDA submission.
IND 64,865	Feb. 10, 2003	Submitted pre-NDA background package.
IND 64,865	April 15, 2003	Submitted CMC information to facilitate early review of the Nexium IV CMC information.
NDA 21-689	Sept. 10, 2003	NDA 21-689 submitted to FDA.
IND 64,865	Dec. 1, 2003	Submitted background package for the Type B meeting to be held Jan. 15, 2004. Purpose of the meeting is to discuss the Phase III clinical development of treatment of acute bleeding peptic ulcer.
NDA 21-689	Dec. 12, 2003	Letter from FDA issuing the PDUFA date for the 10-month review of July10, 2004.
NDA 21-689	Dec. 18, 2003	Submitted partial response to "potential review issues" identified in the Nov. 20, 2003 letter from the Agency. Responded to Issue # 1 by providing additional statistical information for Study SH-

Application No.	Date	Description
		NEP-0006. Responded to Issue # 2 by agreeing to undertake additional compatibility studies.
NDA 21-689	Jan. 8, 2004	Submitted 4-month safety update report for the reporting period May 1, 2003 to Nov. 1, 2003.
IND 64,865	Jan. 12, 2004	FDA responded to the questions submitted in the Dec. 1, 2003 background package. Jan. 15 meeting was canceled. This response is considered the meeting minutes.
NDA 21-689	Feb. 10, 2004	Requested a Type C meeting to discuss AstraZeneca's response to "potential review issues" identified in the Nov. 20, 2003 letter from the Agency.
NDA 21-689	March 24, 2004	Sent FDA via email AstraZeneca's response to questions asked in FDA's March 22 email and March 23 voice mail message.
NDA 21-689	March 29, 2004	Submitted an official copy of AstraZeneca's March 24 email response per request by FDA, Melissa Furness.
NDA 21-689	March 30, 2004	Submitted background package for the April 28 meeting to discuss "potential review issues" from the Nov. 20, 2003 letter.
NDA 21-689	April 1, 2004	Submitted an amendment containing updated stability data.
NDA 21-689	April 9, 2004	Submitted non-clinical amendment containing Study 500204, Study 0140AD, and Ames tests.
NDA 21-689	April 23, 2004	FDA responded to the questions submitted in the March 30 background package.
NDA 21-689	May 6, 2004	Submitted a copy of AstraZeneca's meeting minutes of the teleconference held on April 28 to discuss "potential review issues".
NDA 21-689	June 23, 2004	Submitted a follow-up amendment to the April 1 submission. The amendment contains corrected stability data.
NDA 21-689	June 24, 2004	Submitted clinical amendment containing clinical study reports for Studies D9615C00015 and D9615C00015. Also submitted non-clinical amendment containing study reports for two genetic toxicity studies.
NDA 21-689	July 9, 2004	Received Approvable Letter.
NDA 21-689	Aug. 5, 2004	Submitted a partial response to FDA's July 9 Approvable Letter
NDA 21-689	Aug. 5, 2004	Provided an additional patent, US Patent No. 5,877,192 (granted on April 2, 1999). The patent

Application No.	Date	Description
		covers the method for the treatment of gastric acid-related diseases and production of medication using (-) enantiomer of omeprazole.
NDA 21-689	Sept. 21, 2004	Submitted a response to the July 7, 2004 request that was made by the FDA during the teleconference.
NDA 21-689	Sept. 30, 2004	Submitted a response to the deficiencies identified in the July 9 Approvable Letter.
NDA 21-689	March 23, 2005	FDA provided labeling comments.
NDA 21-689	March 25, 2005	AstraZeneca provided revised carton and vial labeling as well as a package insert.
NDA 21-689	March 31, 2005	NDA 21-689 approved.
NDA 21-689	April 14, 2005	Submitted final printed labeling.

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